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(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM PLC [GB/GB]; 980 Great West Road, CN925.1, Brentford, Middlesex TW8 9G (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): BRANCH, Clive, Leslie [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). NASH, David, John [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow W, Essex CM19 5AW (GB). STEMP, Geoffrey [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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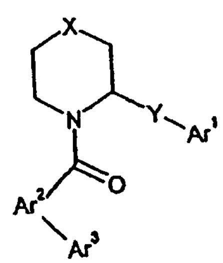
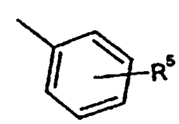
(54) Title: N-AROYL CYCLIC AMINE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS



(I)



(II)

(57) Abstract: According to the invention there is provided compounds of formula (1): Wherein: X represents a bond, oxygen, NR^3 or a group $(CH_2)n$ wherein n represents 1 of 2; Y represents $=(CH_2)qNHC(O)$, $-(CH_2)qO(CH_2)p$, $-(CH_2)qS(CH_2)p$, $-(CH_2)qC(O)(CH_2)p$, $(CH_2)qSO_2(CH_2)p$, $-(CH_2)qCH{=}CH(CH_2)p$, $-(CH_2)pCH(OH)(CH_2)p$, $-C(O)$, $-(CH_2)_3$,$.(CH_2)qNH$, $-(CH_2)qNHCONK$ or $-(CH_2)qCONH$; wherein q represents 1 or 2 and p represents 0 or 1; Ar^1 represents a phenyl, naphthyl or 5 or 6 membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or a bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S any ofwhich can be optionally substituted; Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered'heteroaryl group containing up to 3 heteroatoms selected from N, O and S; Ar^3 represents an optionally substituted R^5.is-O $(CH_2)mNR1R2$ Or $(CH_2)mNR^1$ R^2 each of R^1 and R^2 independently represents a hydrogen atom or an optionally substituted (C_{1-6})alkyl group or R^1 and R^2 together with the nitrogen to which they are attached form part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, or R^1 with at least one CH_2 of . the (CH_2) m portion of the group form a (C_{3-6}) azacycloalkane and R^2 represents hydrogen, an optionally substituted (C_{1-6})alkyl group, piperidine, pyrrolidine, morpholine or with the nitrogen to which they are attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane; R^3 represents hydrogen or optionally substituted (C_{1-6}) alkyl; m represents an integer from '2 to 6; and Ar^3 is attached to Ar^2 ortho to the amide carbonyl group; The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required

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N-AROYL CYCLIC AMINE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS

This invention relates to N-aroyl cyclic amine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; nausea, vomiting, conditions associated with

visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

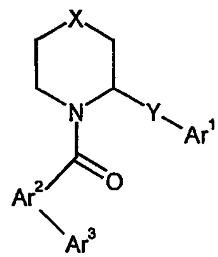
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides N-aroyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders, and/or stroke, particularly ischemic or haemorrhagic stroke, and/or for blocking the emetic response i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577, and WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin receptor antagonists.

According to the invention there is provided compounds of formula (I):



(I)

wherein:

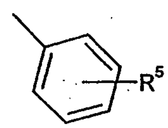
X represents a bond, oxygen, NR^3 or a group $(CH_2)n$ wherein n represents 1 or 2;

Y represents $-(CH_2)qNHC(O)$, $-(CH_2)qO(CH_2)p$, $-(CH_2)qS(CH_2)p$, $-(CH_2)qC(O)(CH_2)p$, $(CH_2)qSO_2(CH_2)p$, $-(CH_2)qCH{=}CH(CH_2)p$, $-(CH_2)pCH(OH)(CH_2)p$, -C(O), $(CH_2)_3$, $-(CH_2)qNH$, $-(CH_2)qNHCONH$, or $-(CH_2)qCONH$; wherein q represents 1 or 2 and p represents 0 or 1;

Ar^1 represents a phenyl, naphthyl or 5 or 6 membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or a bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S any of which can be optionally substituted;

Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar^3 represents an optionally substituted



R^5 is $-O(CH_2)mNR^1R^2$ or $(CH_2)mNR^1R^2$

each of R^1 and R^2 independently represents a hydrogen atom or an optionally substituted(C_{1-6})alkyl group or R^1 and R^2 together with the nitrogen to which they are attached form part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, or R^1 with at least one CH_2 of the $(CH_2)m$ portion of the group form a (C_{3-6})azacycloalkane and R^2 represents hydrogen, an optionally substituted (C_{1-6})alkyl group, piperidine, pyrrolidine, morpholine or with the nitrogen to which they are attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane;

R^3 represents hydrogen or optionally substituted (C_{1-6}) alkyl;

m represents an integer from 2 to 6;

and Ar^3 is attached to Ar^2 *ortho* to the amide carbonyl group;

or pharmaceutically acceptable derivatives thereof.

Examples of 5- to 6- membered heteroaryl groups containing up to 3 heteroatoms selected from N, O and S, include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, piperidine, thiomorpholine, morpholine and piperazine.

When Ar^1 represents a bicyclic heteroaryl it may be selected from isoquinolinyl, quinoxalinyl, benzoxazolyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, benzothienyl, indolyl, benzothiazoyl or quinazolinyl.

Examples of (C_{3-6})azacycloalkanes include piperidine, morpholine, thiomorpholine and piperazine.

Examples of where R^1 with at least one CH_2 of the $(CH_2)m$ portion of the group form a (C_{3-6})azacycloalkane are piperidine and pyrrolidine.

Examples where R^1 with at least one CH_2 of the $(CH_2)m$ portion of the group form a (C_{3-6})azacycloalkane and R^2 with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane are a saturated indolizinyl or quinolizinyl.

When used herein amide carbonyl group refers to the –C(O)N group as shown in compounds of formula (I).

Preferably X is $(CH_2)_n$ wherein n is 1.

Preferably q is 1.

Preferably p is 0.

Preferably Y is $-(CH_2)qNHC(O)$ or $-(CH_2)qNH$.

Preferably Ar^1 is an optionally substituted phenyl or an optionally substituted 5 to 6 membered heteroaryl or bicyclic heteroaryl group, more preferably phenyl, benzofuranyl, quinoxalinyl or pyrimidinyl.

Preferably Ar^2 represents optionally substituted thienyl or thiazolyl.

Preferably R^1 or R^2 are methyl or together with the nitrogen to which they are attached form a 6 membered ring.

Preferably m is 2 to 4.

Optional substituents for the groups R^1, R^2, R^3, Ar^1 Ar^2 and Ar^3 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aR^bN(CH_2)n-$, $R^aR^bN(CH_2)nO-$, $R^aOCO(CH_2)_r$, $R^aCON(R^b)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, n represents an interger from 1 to 4, and r represents zero or an integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n-$ or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a $(C_{3-}$

$_6$)azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

Preferred optional substituents for Ar^2 are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl or (C_{1-4})alkoxy(C_{1-4})alkyl.

Preferred optional substituents for Ar^1 are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})acyl, (C_{1-4})alkoxy(C_{1-4})alkyl or $R^aR^bNCO(CH_2)_r$.

Preferred optional substituents for Ar^3 are halogen or cyano.

In addition Ar^1 may be optionally substituted by a phenyl ring optionally substituted by a halogen, cyano, or C_{1-4}alkanoyl or C_{1-4}alkylsulfonyl group; or by a 5- or 6-membered heterocyclic ring, optionally substituted by a (C_{1-2})alkyl or R^aR^bN- group; wherein R^a and R^b are as defined above.

In the groups Ar^1 and Ar^2, substituents positioned *ortho* to one another may be linked to form a fused ring.

The presence of the group Ar^3 provides the advantage of increasing aqueous solubility.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When used herein the term aryl means a 5- to 6- membered ring, for example phenyl, or a 7- to 8- membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent

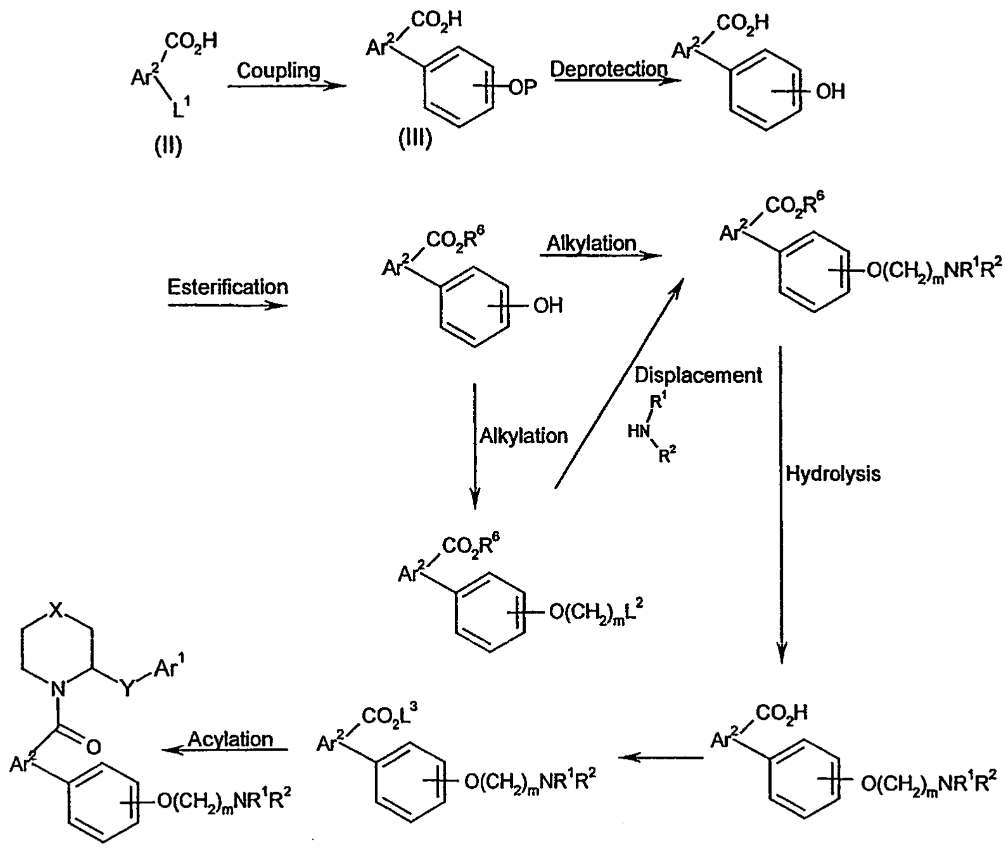
to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and salts thereof. The following scheme details synthetic routes to compounds of the invention.

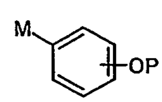
Scheme 1



wherein Ar^1, R^1, R^2, X, Ar^2, Y and m are as defined for compounds of formula (I). P is a protecting group, R^6 is an optionally substituted (C_{1-6}) alkyl group, and L^1, L^2 and L^3 are leaving groups.

Examples of protecting groups P include optionally substituted C_{1-6} alkyl eg. methyl and optionally substituted benzyl. Deprotection conditions will depend on the particular protecting group; for the groups mentioned above these are for example acid (e.g. hydrogen bromide in glacial acetic acid), and catalytic hydrogenolysis in an inert solvent (e.g. using palladium on charcoal in a lower alcohol or ethyl acetate) respectively.

Intermediates (III) can be synthesised using known methods. For example from compounds such as (II) wherein L^1 represents a leaving group such as halogen (preferably iodo or bromo) or trifluoromethanesulphonyloxy- and the coupling step is carried out using known methods e.g. with a reagent



where M is the residue of an organometallic species such as $B(OH)_2$ or trialkylstannyl. Such a process may be carried out in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxan, in the presence of a transition metal catalyst such as $Pd(Ph_3P)_4$. Introduction of the pendant basic group can be achieved using a variety of known methods e.g. direct alkylation with a suitably protected aminoalkyl halide in the presence of a base, such as potassium carbonate, and in an inert solvent such as dimethylformamide. Alternatively, alkylation can be achieved with a suitably protected amino alkyl alcohol under Mitsunobu conditions ie in an inert solvent such as dichloromethane or tetrahydrofuran, in the presence of a phosphine reagent such as triphenylphosphine or tributylphosphine, and an azodicarbonyl reagent such as diethyl azodicarboxylate, diisopropylazodicarboxylate, or 1,1'-azodicarbonyldipiperidine. Alkylation can be achieved stepwise ie. with an optionally suitably protected hydroxyalkyl-halide or alcohol as described above, deprotection and conversion of the hydroxy group to a leaving group L^2, such as halogen (preferably iodo or bromo), trifluoromethanesulphonyloxy, or methanesulphonyloxy, or by direct alkylation with a suitable dihaloalkane (wherein L^2 = halogen directly) in the presence of a base such as potassium carbonate, sodium hydride or potassium *t*-butoxide and in an inert solvent such as dimethylformamide or tetrahydrofuran, followed in each case by displacement with a suitably protected amine, in an inert solvent such as dimethylformamide or tetrahydrofuran optionally in the presence of a base such as potassium carbonate.

Examples of suitable leaving groups L^3 include halogen, hydroxy, OC(=O)alkyl, OC(=O)O-alkyl and OSO_2Me. Acylation may be carried out using a wide range of known conditions, e.g. in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively these steps may be carried out when L^3 represents hydroxy, in which case the reaction takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

Compounds of formula (II) and (III) are known in the literature or can be prepared by known methods. Within the scheme above there is scope for functional group interconversion, and interconversion of protecting groups.

Other compounds of formula (I) containing other R^5 groups can be prepared by analogous processes to that shown in scheme 1 using methods known in the art.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushing's syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. The compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in the treatment of stroke, particularly ischaemic or haemorrhagic stroke. Furthermore the compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in blocking the emetic response.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, sleep disorders, stroke and blocking the emetic response for example nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising

a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochloro-hydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu-NH_2

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1

receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D27 illustrate the preparation of intermediates to compounds of the invention.

Abbreviation used herein are as follow:

MDC represents methylene dichloride

DMSO represents methyl sulphoxide

HATU represents O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

EDC represents 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

DMF represents dimethyl formamide

Description 1(a): 2-(3-methoxyphenyl)-thiophene-3-carboxylic acid

A mixture of 2-iodo-thiophene-3-carboxylic acid (16.8g, 0.066 mol) (M. Takahashi *et al* *Heterocycles*, 1993, 36(8), 1867). 3-methoxybenzene boronic acid (10g,) 0.066 mol), sodium carbonate (30.2g, 0.297 mol), and *tetrakis* (triphenylphosphine) palladium (0) (1.86g, 0.002 mol) in water (150 ml) and 1,2-dimethoxyethane (150 ml) was refluxed under argon for 18 h. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate (2 x 300 ml). The aqueous phase was acidified with 5M hydrochloric acid and the resulting precipitated solid collected by filtration and dried to afford the title compound as a solid (10.6g, 69 %). ^{1}H NMR (D_6-DMSO) δ: 3.78 (3H, s), 6.98 (1H, m), 7.04 (2H, m), 7.33 (1H, t, J = 8 Hz), 7.42 (1H, d, J = 6 Hz), 7.59 (1H, d, J = 6 Hz), 12.65 (1H, br s).

Description 1(b): 2-(4-Methoxyphenyl)-thiophene-3-carboxylic acid

The title compound was prepared, using the method of D1(a), from 2-iodo-thiophene-3-carboxylic acid (16.8 g, 0.066 mol) and 4-methoxybenzene boronic acid (9.2g, 0.06 mol), as a solid (9.96g, 63 %). ^{1}H NMR (D_6-DMSO) δ: 3.79 (3H, s), 6.97 (2H, d, J = 9 Hz), 7.41 (3H, m), 7.52 (1H, d, J = 5 Hz), 12.60 (1H, br s).

Description 1(c): 2-(2-Methoxyphenyl)-thiophene-3-carboxylic acid

The title compound was prepared, using the method of D1(a), from 2-iodo-thiophene-3-carboxylic acid (12.7g, 50 mmol) and 2-methoxybenzene boronic acid (7.6g, 50 mmol), as a solid (7.7g, 66%) after recrystallisation from aqueous ethanol. ^{1}H NMR (D_6-DMSO) δ: 3.71 (3H, s), 6.97 (1H, t, J = 7Hz), 7.06 (1H, d, J = 8 Hz), 7.27 (1H, d, J = 8 Hz), 7.37 (1H, d, J = 5 Hz), 7.34-7.37 (1H, m), 7.55 (1H, d, J = 5 Hz), 12.40 (1H, br. s) .

Description 2(a): 2-(3-Hydroxyphenyl)-thiophene-3-carboxylic acid

D1(a) (1.5g, 6.8 mmol) in 48% w/v hydrogen bromide in glacial acetic acid (30 ml) was refluxed for 24h. with periodic addition of further 48% w/v hydrogen bromide in glacial acetic acid. The resulting mixture was cooled and evaporated; re-evaporation from toluene (x2) gave a solid that was dried *in vacuo* to afford the title compound as a solid (1.5g, 100%). ^{1}H NMR (D_6-DMSO) δ: 7.18 (1H, m), 7.26 (1H, m), 7.36 (1H, m), 7.40 - 7.50 (2H, m), 7.63 (1H, m), 12.6 (1H, br s).

Description 2(b): 2-(4-(Hydroxyphenyl)-thiophene-3-carboxylic acid

The title compound was prepared, as described in D2(a), from D1(b) (3g, 13.6 mmol) as a solid (3g, 100%), and was used without further purification. ^{1}H NMR (D_6-DMSO) δ: *inter alia* 7.18 (2H, d, J = 9 Hz), 7.44 (1H, m), 7.55 (2H, d, J = 9 Hz), 7.65 (1H, m), 12.8 (1H, br s).

Description 2(c): 2-(2-Hydroxyphenyl)-thiophene-3-carboxylic acid

D1(c) (1.0 g, 4.2 mmol) in 48% w/v hydrogen bromide in glacial acetic acid (30ml) was refluxed for 5h. with periodic addition of further 48% w/v hydrogen bromide in glacial acetic acid. The resulting mixture was cooled and evaporated; re-evaporation from toluene and drying *in vacuo* afforded a dark brown solid (0.88g, 100%). ^{1}H NMR (D_6-DMSO) δ: 7.42 (1H, m), 7.51 (1H, d, J = 8 Hz), 7.58 (1H, d, J = 8 Hz), 7.63 (1H, d, J = 5 Hz), 7.88 (1H, d, J = 5 Hz), 7.90 (1H, m).

Description 2(d): 5-(3-Hydroxyphenyl)-2-methylthiazole-4-carboxylic acid

The title compound D2(d) was prepared as a solid (9.8g, 99%) from D14 (10.44g, 0.042 mol) using the method described in D2 (a). ^{1}H NMR (D_6-DMSO) 2.68 (3H, s), 7.15 - 7.25 (1H, m), 7.26 (1H, s), 7.36 (1H, d, J = 8 Hz), 7.47 (1H, t, J = 8 Hz).

Description 3(a): Methyl 2-(3-hydroxyphenyl)-thiophene-3-carboxylate

A mixture of D2(a) (3g, 14.5 mmol) in methanol (100 ml) containing concentrated sulphuric acid (2 ml) was refluxed for 18h., cooled and evaporated. The residue was partitioned between water and MDC. The organic phase was washed with saturated sodium hydrogen carbonate, dried (Na_2SO_4) and evaporated to give the title compound (3g, 93 %). ^1H NMR (D_6-DMSO) δ: 3.68 (3H, s), 6.81 (1H, m), 6.88 (2H, m), 7.21 (1H, t, J = 8 Hz), 7.42 (1H, d, J = 5 Hz), 7.60 (1H, d, J = 5 Hz), 9.59 (1H, s).

Description 3(b): Methyl 2-(4-hydroxyphenyl)-thiophene-3-carboxylate

The title compound (3g, 93 %) was prepared, as described in D3(a) from D2(b) (3g, 14.5 mmol). ^1H NMR ($CDCl_3$) δ: *inter alia* 3.76 (3H, s), 5.25 (1H, br s), 6.83 (2H, d, J = 9 Hz), 7.19 (1H, d, J = 6 Hz), 7.38 (2H, d, J = 9 Hz), 7.48 (1H, d, J = 6 Hz).

Description 3(c): Methyl 5-(3-hydroxyphenyl)-2-methylthiazole-4-carboxylate

The title compound (5.22 g, 50 %) was prepared from D2(d) (9.8g, 0.04 mol) as described for D3 (a). ^1H NMR (D_6-DMSO) δ: 2.67 (3H, s), 3.71 (3H, s), 6.81 - 6.87 (3H, m), 7.22 (1H, t, J = 8 Hz), 9.65 (1H, s).

Description 4(a): Methyl 2-(3-(2-dimethylaminoethoxy)phenyl)-thiophene-3-carboxylate

A mixture of D3(a) (0.4g, 1.8 mmol), 2-(dimethylamino)ethyl chloride hydrochloride (0.31g, 2.2 mmol) and potassium carbonate (1g, 7.2 mmol) in DMF (15 ml) was heated at 100 °C under argon for 18h. The reaction mixture was cooled and evaporated *in vacuo*. The residue was partitioned between ethyl acetate (50 ml) and water (100 ml). The organic phase was washed with water and the aqueous back extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated, re-evaporated from toluene. Chromatography on silica gel with a gradient elution from 50 % ethyl acetate in hexane to 20 % methanol in ethyl acetate afforded the title compound as a gum (0.19g, 34 %). ^1H NMR (D_6-DMSO) δ: 2.22 (6H, s), 2.64 (2H, m), 3.68 (3H, s), 4.08 (2H, m), 6.95 - 7.05 (3H, m), 7.33 (1H, t, J = 8 Hz), 7.45 (1H, d, J = 5 Hz), 7.63 (1H, d, J = 5 Hz).

Description 4(b): Methyl 2-(3-(3-dimethylaminopropoxy)phenyl)-thiophene-3-carboxylate

The title compound (0.214g, 37 %) was prepared, using the method of D4(a), from D3(a) (0.4g, 1.8 mmol) and 3-(dimethylamino)propyl chloride hydrochloride (0.345g, 2.2 mmol). ^1H NMR (D_6-DMSO) δ: 1.85 (2H, m), 2.14 (6H, s), 2.36 (2H, m), 3.68 (3H, s), 4.02 (2H, m), 6.95 - 7.00 (3H, m), 7.32 (1H, t, J = 8 Hz), 7.44 (1H, d, J = 5 Hz), 7.63 (1H, d, J = 5 Hz).

Description 5(a): 2-(3-(2-Dimethylaminoethoxy)phenyl)-thiophene-3-carboxylic acid

The ester D4(a) (0.185g, 0.6 mmol) was refluxed in water (30 ml) containing 2M sodium hydroxide (2ml, 4 mmol) for 18h. The mixture was cooled, neutralised with 2M hydrochloric acid and evaporated *in vacuo*: re-evaporated from toluene. The residue was triturated with 20 % methanol-

MDC, dried (Na_2SO_4) and evaporated to afford the title compound (0.177g, 99 %). ^{1}H NMR (D_6-DMSO) δ: 2.24 (6H, s), 2.67 (2H, t, J = 6 Hz), 3.80 (1H, br s), 4.07 (2H, t, J = 6 Hz), 6.95 (1H, m), 7.04 (1H, d, J = 7 Hz), 7.08 (1H, m), 7.30 (1H, t, J = 8 Hz), 7.37 (1H, d, J = 5 Hz), 7.54 (1H, d, J = 5 Hz).

Description 5(b): 2-(3-(3-Dimethylaminopropoxy)phenyl)-thiophene-3-carboxylic acid

The title compound (0.21g, 99 %) was prepared from D4(b) (0.214g, 0.67 mmol) using the method described in D5(a). ^{1}H NMR (D_6-DMSO) δ: 1.90 (2H, m), 2.31 (6H, s), 2.58 (2H, m), 4.03 (2H, t, J = 7 Hz), 4.80 (1H, br s), 6.90 - 6.93 (1H, m), 7.03 - 7.05 (1H, m), 7.12 (1H, m), 7.26 - 7.30 (2H, m), 7.49 (1H, d, J = 5 Hz).

Description 6(a): Methyl 2-(3-(4-bromobutoxy)phenyl)thiophene-3-carboxylate

A mixture of D3(a) (1.5g, 6.4 mmol), 1,4-dibromobutane (6.91g, 32 mmol) and potassium carbonate (4.43g, 32 mmol) in methyl ethyl ketone (40 ml) was refluxed under argon for 18h. The reaction mixture was cooled, filtered and the filtrate partitioned between ethyl acetate and 1M sodium hydroxide. The organic phase was evaporated and the residue chromatographed on silica gel with a gradient elution of hexane to 50 % ethyl acetate in hexane to afford the title product (0.65g, 28 %). ^{1}H NMR ($CDCl_3$) δ: 1.90 - 2.00 (2H, m),2.00 - 2.15 (2H, m), 3.49 (2H, t, J = 6Hz), 3.75 (3H, s), 4.02 (2H, t, J = 6 Hz), 6.91 (1H, dd, J = 8 and 2 Hz), 7.03 (1H, s), 7.07 (1H, d, J = 5 Hz), 7.20 - 7.35 (2H, m), 7.49 (1H, d, J = 5 Hz).

Description 6(b): Methyl 2-(4-(4-bromobutoxy)phenyl)thiophene-3-carboxylate

The title product (0.8g, 34 %) was prepared from D3(b) (1.5g, 6.4 mmol) and 1,4-dibromobutane (6.91g, 32 mmol) using the method of D6(a). ^{1}H NMR ($CDCl_3$) δ: 1.90 - 2.00 (2H, m), 2.05 - 2.15 (2H, m), 3.51 (2H, t, J = 6 Hz), 3.75 (3H, s), 4.04 (2H, t, J = 6 Hz), 6.92 (2H, d, J = 9 Hz), 7.19 (1H, d, J = 6 Hz), 7.40 - 7.50 (3H, m).

Description 6(c): Methyl 2-(3-(2-bromoethoxy)phenyl)thiophene-3-carboxylate

The title product (1.29g, 59 %) was prepared, using the method of D6(a) from D3(a) (1.5g, 6.4 mmol) and 1,2-dibromoethane (6.01g, 32 mmol). ^{1}H NMR ($CDCl_3$) δ: 3.65 (2H, t, J = 7 Hz), 3.75 (3H, s), 4.32 (2H, t, J = 7 Hz), 6.93 (1H, dd, J = 8 and 2 Hz), 7.07 (1H, s), 7.10 (1H, d, J = 5 Hz), 7.20 - 7.35 (2H, m), 7.49 (1H, d, J = 5 Hz).

Description 7: Methyl 2-(3-(3-chloropropoxy)phenyl)-thiophene-3-carboxylate

To 1-bromo-3-chloropropane (1.28g, 8.1 mmol) and D3(a) (1.26g, 5.4 mmol) in dry DMF (150 ml) under argon was added sodium hydride (0.32g, 60 % dispersion in oil, 8.1 mmol), and the resulting mixture heated at 100 °C for 60h. The reaction was cooled and water added dropwise, followed by evaporation *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl

acetate-pentane mixtures to afford the title compound (1.0g, 60%). ^{1}H NMR (D_6-DMSO) δ: 2.28 (2H, m), 3.71-3.77 (2H, m), 3.75 (3H, s), 4.13 (2H, m), 6.93 (1H, m), 7.05 (1H, s), 7.08 (1H, d, J = 8 Hz), 7.30 (1H, t, J = 8 Hz), 7.25 (1H, d, J = 5 Hz), 7.49 (1H, d, J = 5 Hz).

Description 8(a): Methyl 2-(4-(4-dimethylaminobutoxy)phenyl)-thiophene-3-carboxylate

To D6(b) (0.80g, 2.1 mmol) in DMF (20 ml) was added dimethylamine (0.18g, (2 ml of 2M solution in tetrahydrofuran), 4.0 mmol) followed by potassium carbonate (2.42g, 17.5 mmol) and the resulting mixture heated at 100 °C for 18h. The reaction was cooled and partitioned between MDC and water. The organic phase was evaporated and re-evaporated from toluene. Chromatography on silica gel afforded the title product (0.22g, 30 %). ^{1}H NMR ($CDCl_3$) δ: 1.70 - 1.80 (2H, m), 1.80 - 1.90 (2H, m), 2.38 (6H, s), 2.52 (2H, m), 3.75 (3H, s), 4.03 (2H, t, J = 6 Hz), 6.89 (2H, d, J = 8 Hz), 7.19 (1H, d, J = 6 Hz), 7.42 (2H, d, J = 8 Hz), 7.48 (1H, d, J = 6 Hz).

Description 8(b): Methyl 2-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-thiophene-3-carboxylate

The title compound (1.17g, 96 %) was prepared from D6(c) (1.2g, 3.5 mmol) and piperidine (0.30g, 3.5 mmol) using the method of D8(a). ^{1}H NMR ($CDCl_3$) δ: 1.45 (2H, m), 1.58 - 1.64 (4H, m), 2.51 (4H, m), 2.78 (2H, t, J = 6 Hz), 3.74 (3H, s), 4.13 (2H, t, J = 6 Hz), 6.93 (1H, dd, J = 8 and 2 Hz), 7.00 - 7.10 (2H, m), 7.20 - 7.30 (2H, m), 7.48 (1H, d, J = 6 Hz).

Description 8(c): Methyl 2-(3-(4-dimethylaminobutoxy)phenyl)-thiophene-3-carboxylate

In a similar manner to that described in D8(a) was prepared the title compound from D6(a) which was using without purification in the next step.

Description 9: Methyl 2-(3-(3-dimethylaminopropoxy)phenyl)-thiophene-3-carboxylate

A solution of D7 (1.0g, 3.3 mmol), sodium iodide (3.1g, 20.6 mmol) and dimethylamine (2M solution in DMF, 10 ml, 20.6 mmol) was stirred under argon at 50°C for 48h. The reaction mixture was cooled and evaporated *in vacuo*. The residue was partitioned between MDC and water, and the aqueous layer extracted with MDC. The combined organic phases were dried (Na_2SO_4) and evaporated. Chromatography on silica gel eluting with MDC-methanol mixtures afforded the title product as a brown oil (0.72g, 67%). ^{1}H NMR (D_6-DMSO) δ: 2.16 (2H, m), 2.49 (6H, s), 2.85 (2H, m, J = 6Hz), 3.74 (3H, s), 4.08 (2H, t, J = 6Hz), 6.92 (1H, m), 7.04 (1H, s), 7.07 (1H, m), 7.24 (1H, d, J = 5 Hz), 7.29 (1H, m), 7.48 (1H, J = 5 Hz).

Description 10(a): 2-(4-(4-Dimethylaminobutoxy)phenyl)-thiophene-3-carboxylic acid

A mixture of D8(a) (0.22g, 0.7 mmol) in water (100 ml) containing 2M sodium hydroxide (1ml, 2 mmol) was refluxed for 18h. The cooled solution was neutralised with 5M hydrochloric acid and evaporated. Re-evaporation from toluene (x2) followed by trituration with 20% methanol in MDC afforded the title product (0.24g, 100 %). ^{1}H NMR (D_6-DMSO) δ:1.50 - 1.60 (2H, m), 1.70 - 1.75

(2H, m), 2.14 (6H, s), 2.26 (2H, t, J = 7 Hz), 3.99 (2H, t, J = 7 Hz), 6.74 (1H, d, J = 8 Hz), 6.90 (1H, d, J = 8 Hz), 7.20 (1H, m), 7.31 (1H, m), 7.36 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 8 Hz).

Description 10(b): 2-(3-(2-(Piperidin-1-yl)ethoxy)phenyl)-thiophene-3-carboxylic acid

The title compound (1.15g, 100 %) was prepared from D8(b) (1.17g, 3.4 mmol) as described in D10(a). ^{1}H NMR (D_6-DMSO) δ: 1.36 - 1.40 (2H, m), 1.47 - 1.51 (4H, m), 2.40 - 2.50 (4H, m), 2.66 (2H, t, J = 6 Hz), 4.07 (2H, t, J = 6 Hz), 6.89 (1H, dd, J = 8 and 2 Hz), 7.07 (1H, d, J = 8 Hz), 7.15 (1H, t, J = 2 Hz), 7.24 - 7.28 (2H, m), 7.43 (1H, d, J = 5 Hz).

Description 10(c): 2-(3-(4-Dimethylaminobutoxy)phenyl)-thiophene-3-carboxylic acid

In a similar manner to that described in D10(a) was prepared the title compound from D8(c) which was used without purification in the next step.

Description 11: 3-Dimethylaminopropyl 2-(2-(3-dimethylaminopropoxy)phenyl)-thiophene-3-carboxylate

To D2(c) (0.7g, 3.0 mmol) in dry DMF (40 ml) under argon was added sodium hydride (0.35g, 60% dispersion in oil, 8.8 mmol). After stirring at ambient temperature for 0.3h. under argon, 3-dimethylaminopropyl hydrochloride (0.63g, 4.0 mmol) was added and the resulting mixture heated at 100°C for 72h. The reaction was cooled and water added dropwise followed by evaporation *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous layer was extracted with ethyl acetate and the combined organic phases washed with brine, dried (Na_2SO_4) and evaporated. Chromatography on silica gel eluting with MDC-methanol.0.880 ammonia mixtures afforded the title compound as a brown oil (0.46g, 50%). ^{1}H NMR (D_6-DMSO) δ: 1.62 (2H, m), 1.82 (2H, m), 2.04 (2H, m), 2.13 (6H, s), 2.16 (6H, s), 2.26 (2H, m), 3.97 (2H, t, J = 6 Hz), 4.10 (2H, t, J = 6 Hz), 6.92-6.99 (2H, m), 7.25 (1H, d, J = 5 Hz), 7.29-7.35 (2H, m), 7.49 (1H, d, J = 5 Hz).

Description 12: 2-(2-(3-Dimethylaminopropoxy)phenyl)-thiophene-3-carboxylic acid

The ester D11 (460 mg, 1.24 mmol) was refluxed in water (15 ml) containing 2M sodium hydroxide (0.95 ml, 1.9 mmol) for 16h. The mixture was cooled, acidified with 2M hydrochloric acid, and evaporated *in vacuo*; re-evaporated from toluene. The residue was extracted with 20% methanol-MDC, dried (Na_2SO_4) and evaporated to afford the title compound as a mixture of the acid and 3-dimethylaminopropanol (480 mg, 100%) which was used without further purification. ^{1}H NMR (D_6-DMSO) δ: 1.80 (2H, m), 2.03 (2H, m), 2.68 (6H, s), 2.72 (6H, s), 3.0 (2H, m), 3.07 (2H, m), 3.47 (2H, m), 4.04 (2H, m), 7.0 (1H, t, J = 8 Hz), 7.08 (1H, d, J = 8 Hz), 7.30 (1H, m), 7.37 (1H, m), 7.39 (1H, d, J = 5 Hz), 7.58 (1H, d, J = 5 Hz), 10.2 (1H, br s), 10.5 (1H, br s).

Description 13: Methyl 5-(3-methoxyphenyl)-2-methylthiazole-4-carboxylate

To 3-methoxybenzaldehyde (25g, 0.184 mol) and methyl dichloroacetate (26.3g, 0.184 mol) in diethyl ether (100 ml) under argon at 0 °C was added sodium methoxide (12.42g, 0.23 mol) portionwise, keeping temperature below 15 °C (cf. P. Cacchi *et al Chim. Ind. (Milan)* 1974, *56*, 198). The reaction mixture was warmed to ambient temperature and then refluxed for 1.5h. After cooling to ambient temperature, water was added carefully and the organic phase separated, washed with water, dried (Na_2SO_4) and evaporated to afford methyl 3-chloro-3-(3-methoxyphenyl)-2-oxo-propionate as an oil (44g, 99 %) which was used without purification.

To thioacetamide (13g, 0.17 mol) in ethanol (200 ml) at reflux was added the crude methyl 3-chloro-3-(3-methoxyphenyl)-2-oxo-propionate (40g, 0.17 mol) portionwise over *ca* 0.5h. After a further 0.5h., 0.880 ammonia was added to pH 10, and the reaction mixture cooled to ambient temperature and evaporated. Chromatography of the residue on silica gel eluting with ethyl acetate-hexane mixtures afforded the title product as a solid (23.4g, 52 %). ^{1}H NMR (D_6-DMSO) δ: 2.68 (3H, s), 3.70 (3H, s), 3.78 (3H, s), 7.00 - 7.04 (3H, m), 7.37 (1H, t, J = 8 Hz).

Description 14: 5-(3-Methoxyphenyl)-2-methylthiazole-4-carboxylic acid

A mixture of D13 (23.4g, 0.09 mol) and 2M sodium hydroxide (90 ml, 0.18 mol) in water (300 ml) was heated at 100 °C for 4h, cooled and acidified with 2M hydrochloric acid. The precipitated brown solid was collected by filtration, washed with water and dried to afford the title compound (10.44g, 47%). ^{1}H NMR (D_6-DMSO) δ: 2.67 (3H, s), 3.78 (3H, s), 6.98 - 7.04 (3H, m), 7.34 (1H, t, J = 8 Hz). The aqueous was extracted with MDC, washed with water, dried (Na_2SO_4) and evaporated to give a second batch of title product (5.62g, 25 %).

Description 15 a): Methyl 5-(3-(4-chlorobutoxy)phenyl)-2-methylthiazole-4-carboxylate

To D3(c) (1.74g, 7.0 mmol) in DMF (20 ml) was added 1-iodo-4-chlorobutane (4.6g, 21 mmol) and potassium carbonate (2.89g, 21 mmol) and the mixture heated at 60 °C under argon for 18 h. The reaction mixture was evaporated and partitioned between diethyl ether-ethyl acetate and water; the organic phase was washed with water (x2), dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel eluting with ethyl acetate-hexane mixtures afforded the title compound in *ca* 1:1 mixture with methyl 5-(3-(4-iodobutoxy)phenyl)-2-methylthiazole-4-carboxylate (1g). ^{1}H NMR (D_6-DMSO) δ: 1.70 - 2.00 (4H, m), 2.68 (3H, s), 3.35 (1H, t, J = 7 Hz), 3.70 (3H, s), 3.71 (1H, t, J = 7 Hz), 4.00 - 4.06 (2H, m), 7.00 - 7.03 (3H, m), 7.34 (1H, t, J = 8 Hz).

Description 15(b): Methyl 5-(3-(3-chloropropoxy)phenyl)-2-methylthiazole-4-carboxylate

The title product, containing *ca* 33 % of methyl 5-(3-(3-iodopropoxy)phenyl)-2-methylthiazole-4-carboxylate (1.69g) was prepared from D3(c) (1.74g, 7.0 mmol) as described for D15(a). ^{1}H NMR (D_6-DMSO) δ: *inter alia* 2.14 - 2.22 (2H, m), 2.68 (3H,s), 3.39 (0.66H, t, J = 7 Hz), 3.70 (3H, s), 3.80 (1.34H, t, J = 7 Hz), 4.0 - 4.14 (2H, m), 7.01 - 7.06 (3H, m), 7.34 (1H, m).

Description 16(a): Methyl 5-(3-(4-dimethylaminobutoxy)phenyl)-2-methylthiazole-4-carboxylate

To D15(a) (1g, 3.0 mmol) in DMF (15 ml) containing dimethylamine (2M solution in tetrahydrofuran, 1.5 ml, 3.0 mmol) was added sodium iodide (0.44g, 3.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) and the mixture heated at 50 °C under argon. After several hours further dimethylamine (0.75 ml, 1.5 mmol) was added and heating continued for 18h. The reaction was cooled, evaporated and partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic extracts dried (Na_2SO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate-hexane mixtures afforded the title product (0.51 g, 49 %). ^{1}H NMR ($CDCl_3$) δ: 1.60 - 1.70 (2H, m), 1.75 - 1.85 (2H, m), 2.24 (6H, s), 2.33 (2H, t, J = 7 Hz), 2.74 (3H, s), 3.84 (3H, s), 4.00 (2H, t, J = 7 Hz), 6.94 (1H, dd, J = 7 and 1 Hz), 7.01 - 7.05 (2H, m), 7.30 (1H, t, J = 8 Hz).

Description 16(b): Methyl 5-(3-(3-dimethylaminopropoxy)phenyl)-2-methylthiazole-4-carboxylate

The title compound (0.66g, 38 %) was prepared from D15(b) (1.69g, 5.2 mmol) as described in D16(a). ^{1}H NMR ($CDCl_3$) δ: 1.90 - 2.00 (2H, m), 2.25 (6H, s), 2.45 (2H, t, J = 7 Hz), 2.74 (3H, s), 3.84 (3H, s), 4.03 (2H, t, J = 7 Hz), 6.94 (1H, dd, J = 7 and 1 Hz), 7.02 - 7.04 (2H, m), 7.30 (1H, t, J = 8 Hz).

Description 17(a): 5-(3-(4-Dimethylaminobutoxy)phenyl)-2-methylthiazole-4-carboxylic acid

To D16(a) (0.51g, 1.5 mmol) in methanol (10 ml) and water (30 ml) was added 2M sodium hydroxide (1.5 ml; 3 mmol) and the mixture stirred at ambient temperature for 18h. The reaction mixture was evaporated and the residue taken up in water, neutralised with 2M hydrochloric acid and evaporated. The residue was reevaporated from toluene (x3) and then extracted with 20 % methanol in MDC. The extracts were evaporated to afford the title compound (0.48g, 99 %). ^{1}H NMR (D_6-DMSO) δ: 1.50 - 1.60 (2H, m), 1.65 - 1.80 (2H, m), 2.20 (6H, s), 2.30 - 2.40 (2H, m), 2.51 (3H, s), 3.97 (2H, t, J = 7 Hz), 6.80 (1H, dd, J = 8 and 2 Hz), 7.07 (1H, d, J = 8 Hz), 7.21 (1H, t, J = 8 Hz), 7.34 (1H, m).

Description 17(b): 5-(3-(3-Dimethylaminopropoxy)phenyl)-2-methylthiazole-4-carboxylic acid

The title compound (0.63g, 99 %) was prepared using the method of D17(a) from D16(b) (0.66g, 1.96 mmol). ^{1}H NMR (D_6-DMSO)δ: 1.85 - 2.00 (2H, m), 2.48 (3H, s), 2.70 - 2.80 (2H, m), 3.17 (6H, s), 4.06 (2H, t, J = 7 Hz), 6.90 (1H, m), 6.95 - 7.05 (1H, m), 7.21 (1H, m), 7.29 (1H, m).

Description 18: 2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide

(R)-2-[(S)-2-Aminomethyl-piperidin-1-yl])-2-phenyl-ethanol (20.0g, 0.085 mol) (O. Froelich *et al.* *J. Org. Chem.* 1996, 61, 6700) and triethylamine (13.0ml, 0.094 mol) were dissolved in MDC (500ml), cooled to 0°C and trifluoroacetic anhydride (12.66ml, 0.089 mol) added dropwise. The mixture was warmed to ambient temperature and stirred overnight. The organic phase was washed with water, separated, dried and evaporated. The residue was chromatographed on silica gel, eluting with 0 – 10% (9:1 methanol/ammonia) in MDC to give the title compound (28.0g, 99%) as a yellow oil.

Mass spectrum (API$^+$): Found 331 (MH$^+$). $C_{16}H_{21}F_3N_2O_2$ requires 330. $[\alpha]_D$ -55°@ 28° 1% in chloroform.

Description 19: 2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide

D18 (28.0g, 0.084 mol) was dissolved in ethanol (200ml) containing Pearlmans catalyst (2.0g) and shaken under a hydrogen atmosphere (50psi) at 50°C for 3 hours. The reaction mixture was filtered and solvent removed at reduced pressure. The residue was chromatographed on silica gel, eluting with 0 – 10% (9:1 methanol/ammonia) in MDC, to give the title compound (14.18g, 80%) as a colourless oil. Mass spectrum (API$^+$): Found 211 (MH$^+$). $C_8H_{13}F_3N_2O$ requires 210. $[\alpha]_D$ +18°@ 28° 1% in chloroform. ^{1}H NMR (D_6-DMSO) δ: 1.07 (1H, m), 1.32 (2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, m), 2.70 (1H, m), 3.00 (1H, d), 3.17 (3H, m), 9.30 (1H, br s.)

Description 20: (S)-1-(*t*-Butyloxycarbonyl)-2-[(2,2,2-trifluoroacetamido)-methyl]-piperidine

D19 (14.18g, 0.068 mol) was dissolved in MDC (250ml) and di-*tert*-butyl dicarbonate (14.95g, 0.068 mol) added. The mixture was stirred for 16h., washed sequentially with water, 2M hydrochloric acid and saturated brine, dried and solvent removed at reduced pressure to give the title compound (18.3g, 87%). Mass spectrum (API$^+$): Found 311 (MH$^+$). $C_{13}H_{21}F_3N_2O_3$ requires 310. $[\alpha]_D$ -94°@ 28° 1% in chloroform ^{1}H NMR (D_6-DMSO) δ: 1.27 (1H, m), 1.36, 1.47 (9H, s), 1.49 – 1.58 (5H, m), 2.88 (1H, m), 3.22 (1H, m), 3.49 (1H, m), 3.84 (1H, m), 4.34 (1H, m), 9.42 (1H, br s.).

Description 21: (S)-1-(*t*-Butyloxycarbonyl)-2-aminomethyl-piperidine

D20 (18.2g, 0.06 mol) was dissolved in methanol (500ml) and potassium carbonate added (16.1g, 0.12 mol). After stirring for 16h. solvent was removed at reduced pressure and the residue partitioned between MDC and water. The organic phase was separated, washed with brine, dried and solvent removed at reduced pressure. The residue was chromatographed on silica gel, eluting with 0 – 10% (9:1 methanol/ammonia) in MDC, to give the title compound (8.82g, 72%). Mass spectrum (API$^+$): Found 215 (MH$^+$). $C_{11}H_{22}N_2O_2$ requires 214. $[\alpha]_D$ -32.2°@ 28° 1% in chloroform

^1H NMR ($CDCl_3$) δ: 1.20 – 1.70 (8H, m), 1.46 (9H, s), 2.64 – 2.80 (2H, m), 2.94 (1H, dd), 3.99 (1H, m) and 4.15 (1H, m).

Description 22: (S)-1-(*t*-Butyloxycarbonyl)-2-[(6,7-difluoroquinoxalin-2-ylamino)methyl]-piperidine

D21 (0.607g, 2.8 mmol) and 2-chloro-6,7-difluoroquinoxaline (McQuaid *e. al. J. Med. Chem.* (1992), 35(18), 3319-24) (0.569g, 0.028 mmol) were dissolved in DMF (1ml) and heated at 90 °C for 5 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pale yellow solid (0.460g, 43%). Mass spectrum (API$^+$): Found 379 (MH$^+$). $C_{19}H_{24}F_2N_4O_2$ requires 378.

Description 23: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine

D22 (0.460g, 1.2 mmol) was dissolved in trifluoroacetic acid (10ml) and stirred at ambient temperature for 3 h. The solution was then evaporated and the residue chromatographed on silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in MDC. The title compound was obtained as a pale yellow amorphous solid (0.286g, 85%). Mass spectrum (API$^+$): Found 279 (MH$^+$). $C_{14}H_{16}F_2N_4$ requires 278.

Description 24: (S)-1-(*t*-Butyloxycarbonyl)-2-(3,4-difluorobenzamidomethyl) piperidine

To D21 (1g, 4.7 mmol) and triethylamine (2 ml, 14.1 mmol) in MDC (20 ml) at 0 °C under argon was added 3,4-difluorobenzoyl chloride (0.65 ml, 5.6 mmol) dropwise. The reaction mixture was warmed to ambient temperature overnight and then evaporated. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate, and the organic phase dried (Na_2SO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate-hexane mixtures afforded the title compound as a solid (1.3g, 79 %). Mass spectrum (API$^+$): Found 255 (MH$^+$-^{t}Boc). $C_{18}H_{24}F_2N_2O_3$ requires 354.

Description 25(a): (S)-2-(3,4-Difluorobenzamidomethyl)-piperidine

A solution of D24 (1.3g, 3.6 mmol) in trifluoroacetic acid (10 ml) and MDC (40 ml) was heated at 40 °C for 0.5h., cooled and evaporated. The residue was partitioned between MDC and 2M sodium hydroxide and the organic phase dried (Na_2SO_4) and evaporated to afford the title compound as a solid (0.86g, 92 %). ^1H NMR ($CDCl_3$) δ: 1.10 - 1.9 (7H, m), 2.60 - 2.70 (1H, m), 2.70 - 2.80 (1H, m), 3.07 - 3.10 (1H, m), 3.20 - 3.28 (1H, m), 3.47 - 3.53 (1H, m), 6.72 (1H, br s), 7.00 - 7.26 (1H, m), 7.51 - 7.64 (1H, m), 7.64 - 7.69 (1H, m).

Description 25(b): (S)-((4-Benzofuranyl)carbonylaminomethyl)piperidine

The title compound (0.81g, 95 %) was prepared from D26 (1.26g, 3.5 mmol) using the method of D25(a). ^{1}H NMR ($CDCl_3$) δ: 1.20 - 1.90 (7H, m), 3.60 - 3.70 (1H, m), 2.83 - 2.86 (1H, m), 3.08 - 3.12 (1H, m), 3.30 - 3.36 (1H, m), 3.54 - 3.60 (1H, m), 6.76 (1H, br s), 7.31 - 7.35 (2H, m), 7.58 (1H, d, J = 7 Hz), 7.62 (1H, d, J = 7 Hz), 7.72 (1H, d, J = 2 Hz).

Description 25(c): (S)-2-((2-(5-Bromopyrimidinyl))aminomethyl)piperidine

The title compound (2.02g, 95 %) was obtained from D27 (2.9g, 7.9 mmol) using the method of D25(a). ^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.50 (4H, m), 1.60 - 1.85 (3H, m), 2.55 - 2.65 (1H, m), 2.70 - 2.80 (1H, m), 3.00 - 3.10 (1H, m), 3.23 - 3.29 (1H, m), 3.38 - 3.43 (1H, m), 5.58 (1H, br s), 8.26 (2H, s).

Description 26: (S)-2-((4-Benzofuranyl)carbonylaminomethyl)-1-(*t*-butyloxycarbonyl)piperidine

To D21 (0.8g, 3.7 mmol) in MDC (50 ml) was added benzofuran-4-carboxylic acid (0.75g, 4.5 mmol), followed by EDC (0.86g, 4.5 mmol) and 1-hydroxybenzotriazole (30mg) and the mixture stirred for 18h at ambient temperature. The resulting solution was washed with saturated aqueous sodium hydrogen carbonate and the organic phase applied to a silica gel column and eluted with ethyl acetate-hexane mixtures to afford the title compound as a solid (1.26g, 91 %). Mass spectrum (API$^+$): Found 259 (MH$^+$-^{t}Boc). $C_{20}H_{26}N_2O_4$ requires 358.

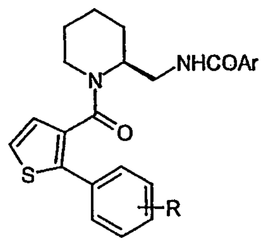
Description 27: (S)-2-((2-(5-Bromopyrimidinyl))aminomethyl)-1-(*t*-butyloxycarbonyl)piperidine

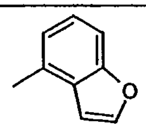
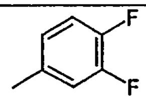
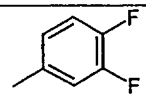
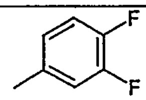
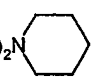
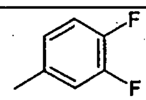
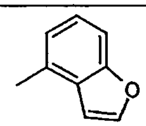
A mixture of D21 (2.2g, 10.2 mmol), 5-bromo-2-chloropyrimidine (1.98g, 10.23 mmol), potassium carbonate (2.82g, 20.4 mmol) and *N,N*-diisopropylethylamine (3.97g, 30.7 mmol) in xylene (40 ml) was heated at 130 °C under argon for 18h. The reaction mixture was filtered, the solid washed with ethyl acetate and the combined organic phase evaporated to a brown oil. Chromatography on silica gel afforded the title compound (2.92g, 77 %). Mass spectrum (API$^+$): Found 271 (MH$^+$-^{t}Boc). $C_{15}H_{23}{}^{79}BrN_4O_2$ requires 370.

Example 1: (S)-2-(3,4-Difluorobenzamidomethyl)-1-((3-(2-(3-(2-dimethylaminoethoxy)phenyl))thiophenyl)carbonyl)piperidine

To the amine D25(a) (0.126g, 0.5 mmol) in MDC (4 ml) at ambient temperature was added the acid D5(a) (0.088g, 0.3 mmol), followed by EDC (0.076g, 0.4 mmol) and 1-hydroxybenzotriazole (0.01g). After shaking for 18h, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate, and the organic phase applied to a pre-packed silica gel cartridge. Gradient elution with 50 % - 100 % ethyl acetate in hexane, followed by ethyl acetate to 10 % methanol in ethyl acetate containing 3 % 0.880 ammonia afforded the title compound (0.079g, 45 %). Mass spectrum (Electrospray LC/MS): Found 528 (MH$^+$). $C_{28}H_{31}F_2N_3O_3S$ requires 527.

In a similar manner were prepared the compounds in Examples 2-7.



Example	R	Ar	Mass Spectrum (Electrospray LC/MS)
2	3-$O(CH_2)_2NMe_2$		Found 532 (MH^+). $C_{30}H_{33}N_3O_4S$ requires 531.
3	3-$O(CH_2)_3NMe_2$		Found 542 (MH^+). $C_{29}H_{33}F_2N_3O_3S$ requires 541.
4	4-$O(CH_2)_4NMe_2$		Found 556 (MH^+). $C_{30}H_{35}F_2N_3O_3S$ requires 555.
5	3-$O(CH_2)_4NMe_2$		Found 556 (MH^+). $C_{30}H_{35}F_2N_3O_3S$ requires 555.
6	3-$O(CH_2)_2$N 		Found 568 (MH^+). $C_{31}H_{35}F_2N_3O_3S$ requires 567.
7	3-$O(CH_2)_3NMe_2$		Found 546 (MH^+). $C_{31}H_{35}N_3O_4S$ requires 545.

Example 8: (S)-2-((4-Benzofuranyl)carbonylaminomethyl-1-((3-(2-(2-(3-dimethylaminopropoxy)phenyl))thiophenyl)carbonyl)piperidine

To D12 (0.110g, 0.3 mmol) in DMF (8 ml) was added HATU (0.121g, 0.32 mmol), followed by *N,N*-diisopropylethylamine (0.114g, 0.9 mmol) and D25(b) (0.077g, 0.3 mmol) and the mixture stirred at ambient temperature under argon for 24h. The reaction mixture was evaporated and the residue partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate; combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate-pentane and ethyl acetate-methanol - 0.880 ammonia mixtures to afford the title compound (0.134g, 82 %). Mass spectrum (Electrospray LC/MS): Found 546 (MH^+). $C_{31}H_{35}N_3O_4S$ requires 545.

Example 9: (S)-2-((2-(6,7-Difluoroquinoxalinyl))aminomethyl)-1-((3-(2-(3-(3-dimethylaminopropoxy)phenyl))thiophenyl)carbonyl)piperidine

A mixture of D5(b) (0.35g, 1.14 mmol) and oxalyl chloride (0.2 ml, 2.30 mmol) in MDC (15 ml) was stirred at 40 °C for 16h., cooled and evaporated. Re-evaporation from MDC (x3) followed by addition of MDC (15 ml) afforded a solution of 3-(2-(3-(3-dimethylaminopropoxy)phenyl))thiophenyl)-carbonyl chloride hydrochloride which was used without purification. 3 ml of this solution was added to D23 (0.06g, 0.22 mmol) in MDC (3 ml) containing triethylamine (0.06 ml, 0.43 mmol) and the mixture shaken at ambient temperature under argon for 16h. Aqueous sodium hydrogen carbonate (2 ml) was added, shaken for 0.5 h., and the organic phase applied directly to a pre-packed silica gel column which was eluted with ethyl acetate-methanol-0.880 ammonia mixtures to afford the title compound (0.016g, 13 %). Mass spectrum (Electrospray LC/MS): Found 566 (MH^+). $C_{30}H_{33}F_2N_5O_2S$ requires 565.

Example 10: (S)-2-((2-(5-Bromopyrimidinyl))aminomethyl)-1-((3-(2-(3-(3-dimethylaminopropoxy)phenyl))thiophenyl)carbonyl)piperidine

The title compound (0.005g, 4 %) was obtained from D25(c) (0.058g, 0.22 mmol) and D5(b) using the method described in E9. Mass spectrum (Electrospray LC/MS): Found 558 (MH^+). $C_{26}H_{32}{}^{79}BrN_5O_2S$ requires 557.

Example 11: (S)-2-(3,4-Difluorobenzamidomethyl)-1-((4-(5-(3-(4-dimethylamino butoxy)phenyl))-2-methyl)thiazolyl)carbonyl)piperidine

To D17(a) (0.10g, 0.3 mmol) in DMF (12 ml) was added D25(a) (0.076g, 0.3 mmol), HATU (0.114g, 0.3 mmol) and *N,N*-diisopropylethylamine (0.067g, 0.3 mmol) and the mixture stirred under argon at ambient temperature for 18h. The reaction mixture was evaporated and partitioned between MDC and aqueous carbonate solution. The organic phase was evaporated and chromatographed on silica gel as described for E8 to afford the title compound (0.012g, 7 %). Mass spectrum (Electrospray LC/MS): Found 571 (MH^+). $C_{30}H_{36}F_2N_4O_3S$ requires 570.

Example 12: (S)-2-(3,4-Difluorobenzamidomethyl)-1-((4-(5-(3-(3-dimethylaminopropoxy)phenyl))-2-methyl)thiazolyl)carbonyl)piperidine

The title compound (0.105g, 61 %) was prepared from D17(b) (0.10g, 0.3 mmol) and D25(a) (0.076g, 0.3 mmol) as described for E11. Mass spectrum (Electrospray LC/MS): Found 557 (MH^+). $C_{29}H_{34}F_2N_4O_3S$ requires 556.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO

BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 μl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 μl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 μM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 μl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 μl. Antagonist or buffer (25 μl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$K_b = IC_{50}/(1+([3/EC_{50}])$$

where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values > 7.1 to 8.4 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

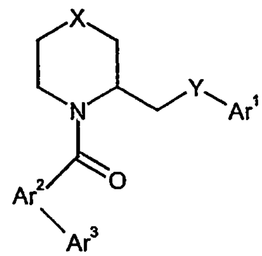
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 6.8 to 8.4 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



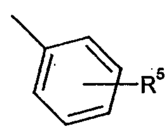
X represents a bond, oxygen, NR^3 or a group $(CH_2)n$ wherein n represents 1 or 2;

Y represents $-(CH_2)qNHC(O)$, $-(CH_2)qO(CH_2)p$, $-(CH_2)qS(CH_2)p$, $-(CH_2)qC(O)(CH_2)p$, $(CH_2)qSO_2(CH_2)p$, $-(CH_2)qCH{=}CH(CH_2)p$, $-(CH_2)pCH(OH)(CH_2)p$, $-C(O)$, $(CH_2)_3$, $-(CH_2)qNH$, $-(CH_2)qNHCONH$, or $-(CH_2)qCONH$; wherein q represents 1 or 2 and p represents 0 or 1;

Ar^1 represents a phenyl, naphthyl or 5 or 6 membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or a bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S any of which can be optionally substituted;

Ar^2 represents an optionally substituted phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar^3 represents an optionally substituted



R^5 is $-O(CH_2)mNR^1R^2$ or $(CH_2)mNR^1R^2$

each of R^1 and R^2 independently represents a hydrogen atom or an optionally substituted(C_{1-6})alkyl group or R^1 and R^2 together with the nitrogen to which they are attached form part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, or R^1 with at least one CH_2 of the $(CH_2)m$ portion of the group form a (C_{3-6})azacycloalkane and R^2 represents hydrogen, an optionally substituted (C_{1-6})alkyl group, piperidine, pyrrolidine, morpholine or with the nitrogen to which they are attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane;

R^3 represents hydrogen or optionally substituted (C_{1-6}) alkyl;

m represents an integer from 2 to 6;

and Ar^3 is attached to Ar^2 *ortho* to the amide carbonyl group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Ar^1 is an optionally substituted phenyl, benzofuranyl, quinoxalinyl or pyrimidinyl.

3. A compound according to claim 1 or 2 wherein Ar^2 represents an optionally substituted thienyl or thiazolyl.

4. A compound according to any one of claims 1 to 3 wherein R^1 or R^2 are methyl or together with the nitrogen to which they are attached form a 6- membered ring

5. The compound of any one of Examples 1 to 12 or a pharmaceutically acceptable salt of any one thereof.

6. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/05773

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4535 A61K31/4525 A61K31/498 A61K31/506 C07D409/06
C07D409/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 58533 A (JOHNS AMANDA ;PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 18 November 1999 (1999-11-18) page 2, lines 26-34 claim 1 ---	1,6,7
Y,P	WO 01 96302 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEV) 20 December 2001 (2001-12-20) claim 1 examples	5-7
A,P	claim 1 ---	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2003	31/03/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fanni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 02/05773

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO 02 44172 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); SMITH ALEXA) 6 June 2002 (2002-06-06) claim 1 examples	5-7
A,P	claim 1	1
Y,P	WO 02 089800 A (JOHNSON CHRISTOPHER NORBERT ;THEWLIS KEVIN MICHAEL (GB); STEMP GEO) 14 November 2002 (2002-11-14) claim 1 examples	5-7
A,P	claim 1	1
X,P	WO 02 090355 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEV) 14 November 2002 (2002-11-14) examples 151,152,181	5-7
A,P	claim 1	1

INTERNATIONAL SEARCH REPORT

PCT/GB 02/05773

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
   because they relate to subject matter not required to be searched by this Authority, namely:

   see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/05773

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9958533	A	18-11-1999	AU	4037799 A	29-11-1999
			CA	2331735 A1	18-11-1999
			WO	9958533 A1	18-11-1999
			EP	1075478 A1	14-02-2001
			US	6372757 B1	16-04-2002
WO 0196302	A	20-12-2001	AU	7247601 A	24-12-2001
			WO	0196302 A1	20-12-2001
			EP	1289955 A1	12-03-2003
WO 0244172	A	06-06-2002	AU	2488502 A	11-06-2002
			WO	0244172 A1	06-06-2002
WO 02089800	A	14-11-2002	WO	02089800 A2	14-11-2002
WO 02090355	A	14-11-2002	WO	02090355 A1	14-11-2002

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 /05773

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 7

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy